Dipyridamole dilates large coronary arteries in conscious dogs

THOMAS H. HINTZE, PH.D., AND STEPHEN F. VATNER, M.D.

ABSTRACT The effects of 0.25 mg/kg dipyridamole on left ventricular (LV) pressures, LV dP/dt, heart rate, aortic pressures, left circumflex coronary blood flow, and left circumflex coronary arterial diameters and on calculations of late diastolic coronary resistance and large coronary cross-sectional area were studied in 15 conscious dogs. Injection of dipyridamole, a drug that has a mechanism of action dependent on myocardial adenosine production, caused sustained increases in mean coronary blood flow (244 ± 28%), large coronary arterial cross-sectional area (28 ± 3.2%), heart rate (32 ± 3.6%), and LV dP/dt (23 ± 3.0%) and reductions in late diastolic coronary resistance (73 ± 2.4%) and mean arterial pressure (14 ± 1.9%). Neither β-adrenergic–receptor blockade alone nor in conjunction with constant heart rate affected the dilation of large coronary arteries to dipyridamole significantly. Ganglionic blockade with hexamethonium also had little effect on the response of large and small coronary vessels to dipyridamole. Surprisingly neither β-adrenergic–receptor nor ganglionic blockade abolished the rise in LV dP/dt observed after dipyridamole. Aminophylline, however, effectively eliminated the dilation of large coronary arteries and resistance coronary vessels in response to dipyridamole. In summary, as long as dipyridamole does not induce severe sustained hypotension it exerts potent effects on both coronary arterial resistance and large coronary arteries in the conscious dog. The coronary dilation is independent of reflex adrenergic activation, but appears dependent on myocardial adenosine production.

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DIPYRIDAMOLE, a drug that has a mechanism of action involving the metabolism of adenosine,1–4 induces sustained, near-maximal vasodilation of coronary resistance vessels.2 However, studies in anesthetized animals5–9 and in man10 suggest that dipyridamole elicits trivial or no dilation of large coronary arteries. These studies are consistent with the hypothesis that dipyridamole acts primarily on coronary resistance vessels,5–9 i.e., the same locus as the proposed site of action of adenosine.11–13 Moreover, the deleterious effects of dipyridamole in the presence of myocardial ischemia have been attributed at least partially to its prominent action on coronary resistance vessels and its limited action on large coronary arteries.6,7 Previous studies have examined the effects of dipyridamole in anesthetized animal preparations5–9 or in normal coronary segments from patients with coronary artery disease.10 The goal of our investigation was to examine the effects and mechanism of action of dipyridamole on instantaneous and continuous measurements of large coronary arterial diameters in intact, normal, conscious animals.

Methods

Mongrel dogs (n = 15) were premedicated with propriopro- mazine HCl (Tranvet; Syntax, Inc.) and surgery was performed by sterile techniques and under general anesthesia with pentobarbital Na (30 mg/kg iv). An incision was made in the left fifth intercostal space and Tygon catheters (Norton Plastics and Syn- thetics Division, Tallmadge, OH) were placed in the descending thoracic aorta and in the left atrium of each dog. Pacing electrodes were sutured on the outflow tract of the right ventricle and on the right atrium. Solid-state pressure gauges (Konigs- berg Instruments, Pasadena, CA) were placed in the apex of the left ventricle. Ultrasonic dimension transducers, 7 MHz piezo- electric crystals (1 × 2 mm × 12 mg) attached to a Dacron backing, were sutured to opposing surfaces of the left circum-

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flex coronary artery with 5-0 suturing (Ethicon, Inc., Somer-
ville, NJ). Alignment of the crystals was maximized at surgery
by monitoring the transmitted ultrasonic signal with an oscil-
scope. In 10 of the dogs a Doppler ultrasonic (n = 9) or electro-
magnetic (n = 1) flow transducer was implanted distally on the
same vessel.

Arterial and left atrial pressures were measured with the im-
planted catheters attached to Statham P23Db strain-gauge ma-
nometers (Statham Instruments, Inc., Oxnard, CA). Left ven-
tricular (LV) pressure was measured with the implanted solid-
state transducers. These transducers were calibrated in vitro
against a mercury manometer and cross-calibrated in vivo with
pressures recorded from the arterial and left atrial catheters.

Instantaneous and continuous measurements of external left cir-
cumflex coronary arterial diameter were obtained with an
im-
proved ultrasonic transit-time dimension gauge. The instrument
measures dimensions by generating a voltage linearly propor-
tional to the transit time of acoustic impulses traveling at the
sonic velocity of 1.55 mm/μsec in tissue. The dimension gauge
was modified to allow measurement of small dimensions in the
arterial system.14–16 Any drift in the dimension gauge, tape
recording system, or the strip chart recorder were eliminated by
frequent calibration during the experiment. The received ultra-
sonic dimension signal was monitored continuously during the
experiment with an oscilloscope. Coronary blood flow was
measured with a Benton Square wave electromagnetic flow
meter (Benton Instruments, Cupertino, California) or a Doppler
flow meter.17 Zero flow reference was established by transient
coronary occlusion with a hydraulic occluder. The Doppler
flow meter has a reliable zero reference.17

Experiments were conducted 1 to 3 weeks after surgery when
the animals were healthy and had been trained to lie on the
table. After control measurements of arterial and LV pressures, heart
rate, LV dP/dt, coronary blood flow, and coronary diameter were
recorded, 0.25 mg/kg iv dipyridamole (Persantine; Boehr-
inger Ingelheim, Inc., Tarrytown, NY) was injected and rec-
cordings were continued for 60 min. Another dose of dipri-
damole was given to 10 dogs either 1 to 2 hr later or on a separate
day after propranolol alone and to seven dogs on another day
after they had received propranolol and while their heart rates
were held constant by electrical pacing. On a separate occasion
in six dogs dipyridamole was injected after aminophylline (1.0
mg/kg/min for 10 min) and in the presence of β-adrenergic-re-
ceptor blockade. Aminophylline was administered after β-

adrenergic-receptor blockade to prevent any complicating in-
creases in myocardial metabolic demand18 and thus secondary
dilation of large coronary arteries,19 which might have obscured
the large coronary dilating effect of dipyridamole. The adequ-
acy of β-adrenergic-receptor and adenosine-receptor blockade
were checked by injection of 0.1 μg/kg isoproterenol and 0.47
μM/kg adenosine, respectively. On a separate day 0.25 mg/kg
dipyridamole was injected into four dogs after ganglionic block-
ade with 30 mg/kg hexamethonium. Dipyridamole was also
administered to two open-chest dogs anesthetized with 30 mg/
kg pentobarbital Na.

Data were recorded continuously on magnetic tape (Bell and
Howell, Inc., Datatape Division, Pasadena, CA) and played
back on a multichannel ink recorder (Gould-Brush, Cleveland,
OH). Mean pressures and coronary diameters were derived with
the use of R-C filters with a 2 sec time constant. LV dP/dt was
derived from the LV pressure signal with Philbrick operational
amplifiers (Teledyne Philbrick, Dedham, MA; frequency re-
sponse of 700 Hz) connected as differentiators. A triangle wave
was substituted for the pressure signal to calibrate the differen-
tiator directly. Heart rate was measured with a cardiotachometer
(Beckman Instruments) triggered by the LV pressure pulse.
Internal coronary cross-sectional area (CSA) was calculated
with known wall volume, blood vessel density, mass of the
artery, and instantaneous external diameter.15 Late diastolic
coronary resistance (LDCR), an index of changes in resistance
coronary vessels, was calculated as the quotient of late diastolic
aortic pressure and late diastolic coronary blood flow. Statistical
analysis was performed by analysis of variance.19

Results
Baseline values are listed in the tables and figures.

Effects of 0.25 mg/kg dipyridamole. The effects of dipri-
damole on phasic changes in coronary blood flow and
diameter are shown in figure 1 and the average
changes for the entire group of dogs studied are shown
in figure 2. The maximal increase in coronary blood
flow occurred 35 ± 4.0 sec after dipyridamole, while
maximal increases in coronary diameter occurred 127
± 11 sec after dipyridamole (figure 2). The maximal
changes from control for all the variables are listed
in table 1. In summary, dipyridamole reduced mean arte-
rial pressure by 14 ± 1.9%, LV systolic pressure by
5.1 ± 1.2%, and LV end-diastolic pressure by 20 ±
4.3% and increased heart rate by 32 ± 3.6%, LV dP/dt
by 23 ± 3.0%, mean coronary blood flow by 244 ±
28%, mean coronary diameter by 6.6 ± 0.7%, and
CSA by 28 ± 3.2%, while LDCR fell by 73 ± 2.4%.
All these changes were significant (p < .01).

Effects of dipyridamole after β-blocking drugs. The
changes in large coronary arterial CSA, mean arterial
pressure, and LDCR after β-adrenergic–receptor
blockade are shown in figure 2. There were no signifi-
cant differences from the unblocked group.

The responses in the seven dogs with constant heart
rates in the presence and absence of β-adrenergic-
receptor blockade are compared in figures 3 and 4.
Dipyridamole reduced mean arterial pressure by 13 ±
1.4% and LV systolic pressure by 4.2 ± 1.8, and
increased LV dP/dt by 21 ± 3.3%, values similar to
those observed without blockade (figure 3). Heart rate
and LV end-diastolic pressure did not change. Coro-
nary blood flow, coronary diameter, and CSA in-
creased by 163 ± 20%, 3.94 ± 0.89%, and 17 ±
3.8%, while LDCR fell by 56 ± 6.3%. The increases
in CSA were not statistically significant, while the
decreases in LDCR were significantly less (p < .02)
after β-adrenergic blockade. It is important to note that
baseline values were different and that LDCR actually
fell to the same level under both conditions. Thus,
holding heart rate constant and administering β-adre-
ergic blockers induced slight alterations from baseline,
but failed to induce major differences in the response to
dipyridamole.

After ganglionic blockade with hexamethonium in
four dogs dipyridamole still reduced mean arterial
pressure 26 ± 4.0% from 99 ± 6.1 mm Hg and
increased LV dP/dt by 21 ± 4.5% from 2228 ± 139 mm Hg/sec, while heart rate did not change from a control of 148 ± 4.0 beats/min. Mean coronary blood flow increased by 161 ± 42% from 27 ± 2.2 ml/min, while coronary diameter increased by 6.2 ± 0.7% from 3.47 ± 0.30 mm and CSA increased by 26 ± 2.9% from a control of 4.73 ± 0.88 mm². LDCR fell by 67 ± 6.5% from 2.58 ± 0.29 mm Hg/ml/min.

After aminophylline in six dogs the dilation of large coronary arteries, the reductions in arterial pressure,
and LDCR and the increases in CSA were markedly reduced not only in magnitude, but more impressively in duration (figure 2).

Effects of 0.25 mg/kg dipyridamole during anesthesia. During pentobarbital anesthesia and left thoracotomy in two dogs, dipyridamole caused a small fall in CSA of 6.9 ± 1.0% from 6.33 ± 2.68 mm². This is contrast to the large increases in CSA that normally occur in response to dipyridamole in the conscious dog.

Discussion

The results of our experiments in normal, conscious dogs indicate that dipyridamole is a potent dilator of large coronary arteries as well as of coronary resistance vessels. The fact that dipyridamole elicits near-maximal decreases in coronary vascular resistance is consistent with the work of other investigators who used a variety of experimental techniques1, 2, 5-9, 10, 20, 21 and with the proposed site of action of adenosine.22 Adenosine exerts its primary effects on small coronary resistance vessels and thus may regulate the increases in coronary flow that accompany an increase in myocardial metabolic demand.12 However, the effects of dipyridamole on large coronary arteries is much more controversial. Most prior studies in anesthetized open-chest animals5-9 or in man, in which normal segments of large coronary arteries distal to a stenosis were studied,10 indicated that dipyridamole did not dilate large coronary arteries. One study conducted in isolated coronary strips did demonstrate a relaxing effect of dipyridamole on large coronary arteries,23 while in another only a relatively small effect was observed.24 We also found that dipyridamole did not increase large coronary vessel CSA in two anesthetized open-chest dogs. Recently Noguchi et al.,9 using the same techniques in anesthetized open-chest dogs, found a reduction in large coronary arterial dimensions with dipyridamole. The difference between the results in conscious and anesthetized animals may be due to a direct or indirect effect of anesthesia on vascular smooth muscle tone25, 26 or to an indirect effect of the high resting heart rate and secondary large coronary arterial dilation ob-

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<td>Mean coronary blood flow (ml/min)</td>
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<td>Coronary diameter (mm)</td>
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<td>Coronary CSA (mm²)</td>
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*All values are different from control, p < .01.
served in the open-chest anesthetized animals.\(^{16}\)

The possibility that the dilation of large coronary arteries induced by dipyridamole was due to increases in myocardial metabolic demand secondary to reflex increases in heart rate and LV dP/dt was considered. To test this possibility, dipyridamole was injected on one occasion after \(\beta\)-adrenergic-receptor blockade alone, on another after \(\beta\)-adrenergic-receptor blockade, and with heart rate constant, and on another after ganglionic blockade with hexamethonium. Under all these conditions the drug had effects on large coronary arteries and on resistance vessels very similar to those observed in the experiments performed in the absence of blockade. Thus, as expected, the mechanism of coronary dilation induced by dipyridamole did not involve reflex adrenergic effects. However, it was surprising that the increases in LV dP/dt with dipyridamole were not prevented by either \(\beta\)-adrenergic or ganglionic blockade. The persistent effects of dipyridamole on LV dP/dt could not be attributed to inad-

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**FIGURE 3.** The effects of 0.25 mg/kg dipyridamole on mean arterial pressure (MAP), heart rate (HR), and LV dP/dt in the absence (open bars) and presence of \(\beta\)-adrenergic-receptor blockade and with HR held constant (solid bars) are compared. Surprisingly, the increases in LV dP/dt were still observed from \(\beta\)-adrenergic-receptor blockade. *Significantly different from predipyridamole control levels (\(p < .05\)).

**FIGURE 4.** The effects of 0.25 mg/kg dipyridamole on LDCR and coronary CSA are compared in the absence (open bars) and presence of \(\beta\)-adrenergic-receptor blockade with constant heart rate (solid bars). While the reductions in LDCR were less, the increases in CSA were not significantly decreased after \(\beta\)-blockade. *Significantly different from predipyridamole control levels (\(p < .05\)).
equate $\beta$-adrenergic blockade. For example, the increases in LV $dP/dt$ after 0.1 $\mu g/kg$ isoproterenol (121 ± 21%) were essentially abolished (14 ± 3.2%) after $\beta$-adrenergic–receptor blockade, yet the rise in LV $dP/dt$ in response to dipyridamole was virtually unaffected. Thus, the increase in LV $dP/dt$ induced by dipyridamole is probably not the result of activation of either autonomic reflexes or the sympathetic nervous system, but rather a direct effect. The results of prior work on the effects of adenosine on myocardial contractility have been conflicting. However, it is interesting to note that a pyrimidopyrimidine derivative (ARL-115), which has a structure similar to that of dipyridamole, has been shown to exert direct positive inotropic activity independent of adrenergic or other reflex effects in anesthetized and conscious dogs.

Dipyridamole is thought to inhibit the uptake of adenosine and thereby potentiate the activity of this powerful endogenous coronary vasodilator. Afonso and Afonso found that the coronary dilating action of dipyridamole and adenosine were inhibited by aminophylline and that dipyridamole potentiated the vasodilating action of adenosine triphosphate. Kubler et al. found that dipyridamole inhibited the degradation of adenosine to inosine by blocking its penetration into myocardial cells, whereas Nott found that dipyridamole potentiated the heart block caused by adenosine at low doses by inhibiting adenosine uptake or, at high doses, by also inhibiting adenosine deamination. Furthermore, Kalsner found that dipyridamole directly inhibited the uptake of adenosine into coronary blood vessels. Prior studies have also indicated that vasodilation of coronary resistance vessels in response to dipyridamole is blocked by the methylnearly antagonines, since the mechanism of vasodilation involves adenosine. Consistent with the findings of these prior studies, we observed that the effects of dipyridamole on resistance coronary vessels were largely eliminated by the preadministration of aminophylline. Furthermore, we found that the dipyridamole-induced dilation of large coronary arteries was blocked by aminophylline.

It is conceivable that the dilation of large coronary arteries is in part secondary to the large increases in coronary blood flow that occur after the administration of dipyridamole. In prior studies in which a large atrioventricular shunt was opened in the femoral circulation a dramatic flow-dependent increase in large arterial dimensions was observed. Gerova et al. found large coronary artery dilation when flow increased markedly with opening of an atrioventricular shunt. We have recently observed that the reactive dilation of large coronary arteries after brief periods of coronary occlusion and myocardial ischemia can be eliminated by preventing reactive hyperemia on release of the coronary occlusion; however, the increase in large coronary arterial dimensions secondary to increasing heart rate or adenosine administration is only partially attenuated by this technique. It is unlikely that the mechanism of the large coronary arterial dilation in our study was due to the increased flow velocity only since in previous studies in anesthetized animals marked increases in coronary blood flow occurred with dipyridamole, yet the resistance of large coronary arteries and large coronary artery diameter were not changed by the drug.

The deleterious actions of dipyridamole in the presence of regional myocardial ischemia have been attributed to its prominent effects on small coronary vessels, which result in a massive fall in resistance in the nonischemic zone and diversion of blood flow from the ischemic area. Since coronary collateral channels are thought to behave like large coronary arteries, and some prior studies failed to observe large coronary arterial dilation with dipyridamole, it was postulated that dipyridamole elicits a "steal" by dilating coronary resistance vessels and not the large collateral vessels that are crucial in maintaining blood flow to ischemic myocardium. Studies by Winbury et al. and Weiss and Winbury have suggested that dipyridamole does not increase oxygen delivery to the endocardium, as opposed to nitroglycerin, which has this favorable effect. Dipyridamole also does not increase retrograde coronary flow. These studies were also conducted in anesthetized animals. In contrast, studies by Rembert et al. in conscious dogs have shown that dipyridamole shifted the distribution of blood flow to the endocardium.

Since our experiments were conducted in healthy, conscious dogs, it is difficult to extrapolate our results to the situation of regional myocardial ischemia. However, a recent study by Blumenthal et al. showed that dipyridamole reduced experimental infarct size considerably, and that this was attributable to an increase in coronary collateral flow as measured with the radioactive microsphere technique. These authors believe that in previous studies with dipyridamole exacerbation of myocardial ischemia resulted, due primarily to the large fall in coronary perfusion pressure caused by an excessive dose of dipyridamole. Indeed, aortic pressure is a principal determinant of coronary collateral blood flow and transmural myocardial perfusion. The reduction in mean arterial pressure observed and the dose of dipyridamole used in the study...
by Blumenthal et al. are similar to those in our study and in other studies in man. Thus, the extent of reduction in coronary perfusion pressure could well be the critical factor in determining whether dipyridamole dilates large coronary arteries and collateral channels.

In summary, dipyridamole dilates large and small coronary resistance vessels in the conscious dog. These actions are exclusive of changes in myocardial metabolic demand or β-adrenergic mechanisms, but appear dependent on the production of adenosine. If the collateral channels behave as large coronary arteries and if the responses in the presence of ischemic heart disease are similar to those in the normal animal, then any potential deleterious effect of dipyridamole in this ischemic setting must be explained by some mechanism other than failure to dilate large coronary arteries.

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References

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